Synthetic cannabinoids and acute kidney injury

Weeraporn Srisung, MD, Faisal Jamal, MD, and Sharma Prabhakar, MD

Synthetic cannabinoids (SCB) are a family of chemicals that bind to cannabinoid receptors and cause psychoactive effects. Over the past few years, they have been increasingly used for recreational purposes, especially by young adults, and have been reported to have many adverse effects. Acute kidney injury (AKI) has been recently reported; the pathophysiology of SCB-induced AKI is unknown. We report three cases of AKI in the setting of SCB use. The peak serum creatinine levels ranged from 3.0 to 5.7 mg/dL; one patient required hemodialysis. SCB can induce AKI.

Recent literature has documented reports of acute kidney injury (AKI) in association with the use of synthetic cannabinoids (SCB); however, the pathogenesis of this complication is not known. We report three cases of SCB-induced AKI in patients from our medical center.

CASE PRESENTATION

Clinical findings in all three patients are summarized in *Table 1*. Case 1 was a 31-year-old man with depression and hypertension who presented after a physical assault. Concomitantly, he was found to have AKI in the setting of SCB use. He was not in hypertensive crisis on presentation. His creatine kinase (CK) was normal, and his renal function improved after supportive treatment. Case 2 was a 32-year-old man who presented with alteration of consciousness. He had been abusing methamphetamine, opioids, and SCB. Neurological examination showed no focal findings; his pupils were normal. He regained consciousness on the next day. Altered mental status was attributed to methamphetamine overdose. He subsequently developed AKI. His CK level was 3987 IU/L. The patient required one session of hemodialysis before his kidney function recovered. Case 3 was a 31-year-old man with depression who presented with combative behavior. The patient abused SCB daily until 2 days prior to admission. He was found to have AKI with eosinophiluria and without eosinophilia. His serum creatinine (SCr) improved the next day with intravenous fluid hydration. He denied regular usage of nonsteroidal antiinflammatory drugs (NSAIDS). *Figure 1* illustrates trends in SCr in all three patients.

Table 1. Certain clinical findings in the three patients with synthetic cannabinoid–induced acute kidney injury

Variables	Case 1	Case 2	Case 3
Age (years)	31	32	31
Psychiatric disorder	+	0	+
Hypertension	+	0	0
Tobacco use	+	+	+
Methamphetamine use	+	+	0
Opioid use	0	+	0
Duration of SCB use (years)	3	5	Unclear
Last use of SCB (days prior to admission)	1	0.5	2
Oliguria	0	+	0
Peak blood urea nitrogen (mg/dL)	26	24	30
Peak serum creatinine (mL/dL)	3.0	5.7	3.5
Creatine kinase (IU/L)	255	3987	1137
Fractional excretion of sodium (%)	1.99	2.13	2.14
Fractional excretion of urea (%)	61.9	–	–
Hydronephrosis	0	0	0
Dialysis	0	+	0

+ indicates present; 0, absent; –, information not available.

DISCUSSION

SCB use is becoming more problematic in contemporary society. Its harmful effects are not well understood by the public and the medical community, and the incidence of complications related to SCB is high. The Drug Abuse Warning Network reported that among patients aged 12 to 29, 11,406 emergency department visits were specifically linked to SCB among the approximately 2,300,000 visits that involved drug misuse or abuse (1). In 2012, SCB was used by 11.3% of high school seniors (2).

From the Department of Internal Medicine (Srisung, Jamal, Prabhakar) and the Division of Nephrology (Jamal, Prabhakar), Texas Tech University Health Sciences Center, Lubbock, Texas.

Corresponding author: Weeraporn Srisung, MD, Department of Internal Medicine, Texas Tech University Health Sciences Center, 3601 4th Street, Lubbock, TX 79430 (e-mail: weeraporn.srisung@ttuhsc.edu).
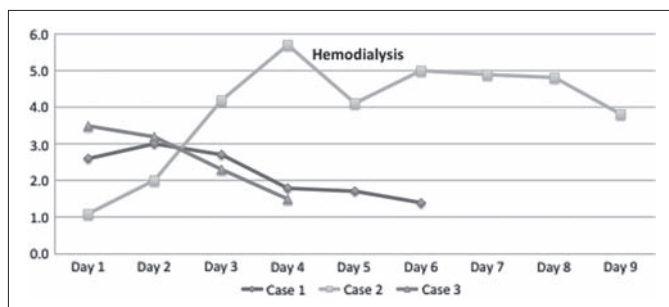
Figure 1. Trends in serum creatinine (mg/dL) in the three patients throughout their hospitalizations.

SCB and their agonists were invented for research purposes (3). Several side effects of these substances have been reported in the literature (1, 3).

All three of our patients reported regular usage of SCB either the day of or within 3 days of their hospitalization. Careful clinical assessments suggest that SCB is likely the etiology of renal impairment in these patients. Because conventional practice suggests mainly observation in patients whose clinical courses are consistent with acute tubular necrosis (ATN), kidney biopsies were not performed in these patients. Since no other likely causes of ATN were present in these cases, SCB was left as the most likely cause of AKI.

In case 1, the patient developed AKI from an intrinsic renal condition, given that the fractional excretion of sodium and fractional excretion of urea excluded a prerenal cause and renal ultrasound excluded a postrenal cause of AKI. Although this patient concomitantly used intravenous methamphetamine, his CK level did not indicate the presence of rhabdomyolysis, which is the usual pathophysiologic mechanism of AKI caused by it (4). Case 2 was a similar scenario. Although renal biopsy was not obtained, the results of other investigations pointed toward ATN as the cause of AKI. The patient's CK level of 3987 IU/L should not have caused him to have such profound AKI that required dialysis (5, 6). In case 3, no concomitant substance usage was involved. He also had a mildly elevated CK level, at 1137 IU/mL, which was also too mild to cause AKI. Without any other offending agents leading to AKI, we believe that SCB could have affected his kidney function, although acute interstitial nephritis (AIN) is more likely to be the mechanism of AKI than ATN in this case given the presence of eosinophiluria.

Due to the reasons above, we strongly suspect that SCB has an association with AKI in these cases. Although the causal relationship and pathophysiologic mechanism have not been conclusively established, the temporal relationship between the use of SCB and AKI, and the lack of evidence for other causes of AKI, strongly support the association. ATN is likely the type of AKI in cases 1 and 2, although AIN was suspected in case 3. Unfortunately, we do not have a histologic diagnosis. All patients in our case series regained their baseline kidney function, and only one patient required hemodialysis before the resolution of AKI, indicating that reversibility of SCB-induced AKI is very possible.

SCB-induced AKI has been previously discussed in the literature. Bhanushali et al reported four cases of AKI associated with SCB (7). Three out of four of their patients underwent kidney biopsy, which showed findings consistent with ATN, i.e., tubular cell apical blebbing and cytoplasmic vacuolization. Kidney function in all four patients improved without dialysis. Later, the Centers for Disease Control and Prevention reported 16 cases of SCB-induced AKI in multiple states (8). ATN was demonstrated on 6 renal biopsies out of 8 that were performed, and AIN was found in 3 of 8 biopsies; these findings are compatible with our cases. Interestingly, the product used by 5 of 16 patients, with two of them reporting the use of the same product, contained XLR-11 or [1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone. Additionally, XLR-11 and/or its metabolites were found in 5 of 7 patients in whom clinical specimen analysis was performed. Thus, this raises the possibility that XLR-11 or its metabolites might be the culprit causing AKI in this group of patients, although an unidentified contaminant might be related to AKI in these subjects.

XLR-11 is a fluorinated UR-144 analog that has recently been encountered in the designer drug market (9). XLR-11 and its derivatives share a core indole 2,2,3,3-tetramethylcyclopropyl (TCMP) ring, as shown in *Figure 2*. It was shown that XLR-11 and UR-144 had Δ9-THS-like activity in animals and bind to the brain cannabinoid receptor (CB1 receptor) in in vitro studies. CB1 receptors are also expressed in kidney cells, including podocytes and proximal tubule cells (10–12), and we suggest that the AKI related to SCB might be related to CB1 receptors in the kidneys. There are limited data on the CB1 receptor and kidney function. However, blockade of CB1 receptors has been shown to have protective effects on renal function and ameliorate albuminuria in certain groups of mice (10, 11, 13).

Wohlfarth et al studied the metabolism of XLR-11 by incubating it with pooled human hepatocytes and identifying metabolites after 1 and 3 hours using high-resolution mass spectrometry followed by information-dependent acquisition triggered product ion scans with dynamic background subtraction
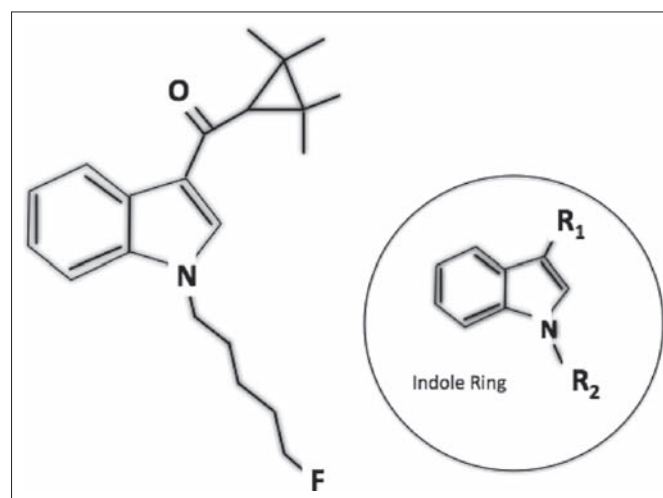

Figure 2. XLR-11 and its core indole ring's structures.

and mass defect filters (14). These experiments demonstrated that XLR-11 undergoes phase I and II metabolism, producing more than 25 metabolites (including 7 major metabolites) resulting from hydroxylation, carboxylation, hemiketal and hemiacetal formation, etc. ATN remains the most common pathology found in kidney biopsies and in clinical scenarios in reports (7, 8). However, even with the knowledge of XLR-11's structural elements and its metabolites, it remained questionable how SCB could cause AKI. Intracellular processes that are involved in drug- or substance-induced tubular cell toxicity include formation of free radicals, tubular transport interference, increase in oxidative stress, or impairment of mitochondrial function. Therefore, we hypothesize that SCB-induced AKI may involve one or more of the above-mentioned processes. Rhabdomyolysis is less likely in the reported cases, given the normal CK level in case 1 and the mildly elevated CK levels in cases 2 and 3.

1. Substance Abuse and Mental Health Services Administration. Drug-related emergency department visits involving synthetic cannabinoids. *The DAWN Report,* December 4, 2012:1–5. Available at http://archive.samhsa.gov/data/2k12/DAWN105/SR105-synthetic-marijuana.pdf.
2. National Institute on Drug Abuse. *Monitoring the Future Survey, Overview of Findings 2012.* Available at http://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future/monitoring-future-survey-overview-findings-2012.
3. Huffman JW. Cannabimimetic indoles, pyrroles and indenes. *Curr Med Chem* 1999;6(8):705–720.
4. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician* 2008;78(6):743–750.
5. Kenny JE. Creatinine kinase: how much is too much? *Clinical Correlations,* November 3, 2010. Available at http://www.clinicalcorrelations.org/?p=3390.
6. Latham J, Campbell D, Nichols W, Mott T. Clinical inquiries. How much can exercise raise creatine kinase level—and does it matter? *J Fam Pract* 2008;57(8):545–547.
7. Bhanushali GK, Jain G, Fatima H, Leisch LJ, Thornley-Brown D. AKI associated with synthetic cannabinoids: a case series. *Clin J Am Soc Nephrol* 2013;8(4):523–526.
8. Centers for Disease Control and Prevention. Acute kidney injury associated with synthetic cannabinoid use—multiple states, 2012. *MMWR Morb Mortal Wkly Rep* 2013;62(6):93–98.
9. Drug Enforcement Administration. *UR-144 (TCMP-018; KM-X1) and XLR11 (5-F-UR-144).* 2013. Available at http://www.deadiversion.usdoj.gov/drug_chem_info/spice/spice_ur144_xlr11.pdf.
10. Nam DH, Lee MH, Kim JE, Song HK, Kang YS, Lee JE, Kim HW, Cha JJ, Hyun YY, Kim SH, Han SY, Han KH, Han JY, Cha DR. Blockade of cannabinoid receptor 1 improves insulin resistance, lipid metabolism, and diabetic nephropathy in db/db mice. *Endocrinology* 2012;153(3):1387–1396.
11. Barutta F, Corbelli A, Mastrocola R, Gambino R, Di Marzo V, Pinach S, Rastaldi MP, Perin PC, Gruden G. Cannabinoid receptor 1 blockade ameliorates albuminuria in experimental diabetic nephropathy. *Diabetes* 2010;59(4):1046–1054.
12. Bach LA. Diabetic nephropathy: do cannabinoids contribute? *Endocrinology* 2012;153(3):1008–1009.
13. Janiak P, Poirier B, Bidouard JP, Cadrouvele C, Pierre F, Gouraud L, Barbosa I, Dedio J, Maffrand JP, Le Fur G, O'Connor S, Herbert JM. Blockade of cannabinoid CB1 receptors improves renal function, metabolic profile, and increased survival of obese Zucker rats. *Kidney Int* 2007;72(11):1345–1357.
14. Wohlfarth A, Pang S, Zhu M, Gandhi AS, Scheidweiler KB, Liu HF, Huestis MA. First metabolic profile of XLR-11, a novel synthetic cannabinoid, obtained by using human hepatocytes and high-resolution mass spectrometry. *Clin Chem* 2013;59(11):1638–1648.